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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/734,563
Filing Date: December 12, 2003
Appellant(s) : Sorge et al.

Timothy B. Donaldson
For Appellant

EXAMINER'S ANSWER

This is in response to the final office action, mailed 2/28/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows:

Appellants have asked that the provisional rejection on the grounds of nonstatutory obviousness-type double patenting over copending Application No. 10/298,680, be held in abeyance until one of the two applications in question is deemed to be in condition for allowance.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Evidence relied upon by the examiner in the rejection of the claims under appeal is an alignment of amino acids 81-96 of SEQ ID NO:83-108, included as an Appendix at the end of the Answer.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 12-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-10 and 12-21 are directed to all possible Archaeal DNA polymerases and compositions and kits comprising said Archaeal DNA polymerase, wherein said Archaeal DNA polymerase comprises at least one amino acid mutation in an exol, exo II or exo III motif or a combination thereof and an amino acid mutation at position V93 in an amino acid sequence of SEQ ID NO: 89, wherein said Archaeal DNA polymerase is deficient in 3'-5' exonuclease activity. The rejected claims are interpreted as not requiring any structure beyond that of the specified mutation positions only. The specification, however, only provides that Archaeal DNA polymerases and compositions and kits comprising said Archaeal DNA polymerase, wherein said Archaeal DNA polymerase comprises the amino acid sequence of the Pfu DNA polymerase, SEQ ID NO: 89, with an amino acid mutation in an exol, exo II or exo III motif or a combination thereof and an amino acid mutation at position V93 in the amino acid sequence of SEQ ID NO: 89, wherein said Archaeal DNA polymerase is deficient in 3'-5' exonuclease activity, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species that would put one in possession of the genus of all possible mutant Archaeal DNA polymerases comprising an amino acid mutation in an exol, exo II or exo III motif or a combination thereof and an amino acid mutation at position V93 in an amino acid sequence of SEQ ID NO:89,

that are deficient in 3'-5' exonuclease activity. The specification also fails to describe additional representative species of these mutant DNA polymerases by any identifying structural characteristics or properties other than the activities recited in the claims, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Appellants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Appellants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-10 and 12-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a Pfu DNA polymerase comprising the amino acid sequence of SEQ ID NO: 89 with an amino acid substitution at position V93, does not reasonably provide enablement for any possible Archaeal DNA polymerase comprising at least one amino acid mutation in an exoI, exo II or exo III motif and another amino acid mutation at position V93 in an amino acid sequence selected from SEQ ID NO:89, wherein said polymerase is deficient in 3'-5' exonuclease activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-10 and 12-21 are so broad as to encompass any possible polymerase that originated as an Archaeal DNA polymerase and further comprises at least one amino acid mutation in an exoI, exo II or exo III motif and another amino acid mutation at position V93 in an amino acid sequence selected from SEQ ID NO:89, wherein said polymerase is deficient in 3'-5' exonuclease activity. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant DNA polymerases broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, place minor if any structural limits on the claimed mutant DNA polymerases. The claimed genus of DNA polymerase is interpreted as not being structurally limited beyond the necessary mutation positions and this includes the vast types of mutations that may occur at these mutation positions. These referred to mutations include but are not limited to one or more amino acid substitutions, one or more amino acid insertions, a truncation or an internal deletion (see specification page 11, lines 2-4) or any additional type of post-translational modification at these referred to amino acid positions. Since

the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those instantly disclosed mutant Pfu DNA polymerases that are deficient in 3'-5' exonuclease activity and comprise the amino acid sequence of SEQ ID NO: 89 with an amino acid substitution mutation at position V93 of SEQ ID NO:89.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any mutant DNA polymerase comprising the amino acid sequence of SEQ ID NO: 89 and comprising at least one mutation in an exo I, II or III motif and another at position V93, that is deficient in 3'-5' exonuclease activity, because the specification does not establish: (A) regions of the protein structure

Art Unit: 1652

which may be modified and the type of modifications that may be made without effecting 3'-5' exonuclease activity; (B) the general tolerance of Archaeal DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for identifying and modifying an amino acid at V93 of said Archaeal DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to maintain the desired activity and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those mutant DNA polymerases of the claimed genus having the claimed activities.

Thus, Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any Archaeal DNA polymerase comprising at least one amino acid mutation in an exoI, exo II or exo III motif and another amino acid mutation at position V93 in an amino acid sequence selected from SEQ ID NO:89, wherein said polymerase is deficient in 3'-5' exonuclease activity. The scope of the claims must bear a reasonable correlation with the scope of enablement

(In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

(10) Response to Argument

Prior to their traversal, Appellants note that the Examiner required election of a single member of the group of SEQ ID NOs. 83-108 recited in claims 1-7 and Appellants elected with traverse the wild type Pfu DNA polymerase of SEQ ID NO. 89. Appellants submit that the Examiner's rejections under 35 U.S.C. § 112, first paragraph for lack of written description and lack of enablement appear applicable to the entire claimed genus and not merely to the elected sequence. Appellants submit that therefore, in response, Appellants address the 112, first paragraph rejections with respect to both the elected species (SEQ ID NO. 89) and the claimed genus (SEQ ID NOs. 83-108).

Written Description

Appellants continue to submit that for the reasons discussed below, the specification provides a sufficiently detailed description of the claimed genus by structure and a known and disclosed correlation between structure and function, so as to distinguish it from other mutant Archaeal DNA polymerases, as well as through a description of numerous representative members of the genus, such that one of skill in

the art would recognize that Appellants were in possession of the claimed invention at the time the application was filed.

With respect to the elected representative species, Appellants submit that Claim 1 is directed to a mutant Archaeal DNA polymerase comprising: at least one amino acid mutation in the exo I motif, and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108, where said mutant Archaeal DNA polymerase is deficient in 3' to 5' exonuclease activity. Appellants submit that Claims 2-7 are similarly directed to mutant Archaeal DNA polymerases with an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108 and deficient in 3' to 5' exonuclease activity but further recite at least one amino acid mutation in the exo II motif (claim 2), the exo III motif(claim 3), each of the exo I and exo III motifs (claim 4), each of the exo II and exo III motifs (claim 5), each of the exo I and exo II motifs (claim 6), and each of the exo I, exo II, and exo III (claims 7).

Appellants reference to the above claims is appreciated and for the purpose of proper analysis of the description of the claimed subject matter, the breadth of these claims is discussed herein. Claim 1, for this purpose is directed to a mutant Archaeal DNA polymerase comprising: at least one amino acid mutation in the exo I motif, and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108, where said mutant Archaeal DNA polymerase is deficient in 3' to 5' exonuclease activity. It is understood that the claimed "Archaeal DNA polymerase" is deficient in 3'-5' exonuclease activity. Thus as Appellants have submitted that the Archaeal DNA polymerases have a 3' to 5' exonuclease activity (See appellants

specification at page 1, line 22) appellants claim 1 is clearly drawn to a “mutant Archaeal DNA polymerase”, which thus is not subject to any of the structural limitations of an “Archaeal DNA polymerase”, because it is mutated such that it is no longer an “Archaeal DNA polymerase”. Claim 1 further recites that the claimed "Archaeal DNA polymerase" “compris(ing)es at least one amino acid mutation in the exol motif and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108”. Thus the “mutant Archaeal DNA polymerase” comprises at least one amino acid mutation in the exol motif and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108. Thus clearly the claimed mutant Archaeal DNA polymerase comprises at least two mutations that are not normally found in an Archaeal DNA polymerase. Appellants reference to “an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108, is interpreted as the referred to amino acid mutation is at position V93, in which V93 is referenced to SEQ ID NOs. 83-108. The reference to SEQ ID NOs. 83-108 is not interpreted as relevant beyond providing a reference to "V93" and perhaps a point of origin of the mutated DNA polymerase, but clearly the breadth of the genus of claimed DNA polymerase mutants is not interpreted as limited to any of SEQ ID NOs. 83-108. Thus appellants claim 1 is drawn to an Archaeal DNA polymerase" which is deficient in 3'-5' exonuclease activity and comprises at lease two mutations that do not normally occur in an Archaeal DNA polymerase. One of the “at least one mutation” ’s must be in motif I of the 3'-5' exonuclease domain and the other mutation must be at V93 of the elected SEQ ID NO:89 or the non-elected SEQ ID NOs:83-88 and 90-108. It seems

that it should further be noted here that while the elected SEQ ID NO: 89 has a Valine residue at position 93 and thus a V93, which may according to appellants be further mutated, of the additional 25 SEQ ID NOs. referred to (i.e. SEQ ID NO. 83-88 and 90-108) 9 of these SEQ ID NOs do not have a valine at position 93 (i.e. SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:107 and SEQ ID NO:108, See appendix alignment of Appellants SEQ ID NOs 83-108). Thus 9 of the 25 non-elected SEQ ID NOs, greater than a third of the referenced group do not have a V93.

Additionally it is noted that appellants claim 1 is drawn to an "Archaeal DNA polymerase" comprising at least one mutation in the exoI motif and an amino acid mutation at V93 in the referred to amino acid sequence. These referred to mutations include but are not limited to one or more amino acid substitutions, one or more amino acid insertions, a truncation or an internal deletion (see specification page 11, lines 2-4). Appellants further specify that, as used herein, "mutant" polymerase refers to an Archaeal DNA polymerase, as defined herein, comprising one or more mutations that alter one or more activities of the DNA polymerase, for example, DNA polymerization, 3'-5' exonuclease activity or base analog detection activities (specification page 10, lines 23-26).

Thus, claim 1 is interpreted as being drawn to a mutant Archaeal DNA polymerase which is deficient in 3'-5' exonuclease activity and comprises at least one amino acid mutation in the exo I motif, and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108. Thus for those reasons

stated previously and above, Appellants claim 1 is drawn to a mutant Archaeal DNA polymerase which is deficient in 3'-5' exonuclease activity and comprising at least one mutation in the exoI motif and an amino acid mutation at V93. Thus appellants claim 1 is drawn to a mutant DNA polymerase in which the only specified structural limitations are in regard to mutation positions (i.e. at least one amino acid mutation in the exoI motif and an amino acid mutation at V93). Outside of the structural limitations associated with each of the required two "at least one amino acid mutation" 's, the claimed DNA polymerase has no structural limitations. It is further noted that claims 2-7 are interpreted analogously as claim 1, as discussed above, however, with respect to the exoII and exoIII motifs and combinations of the exoI, exoII and exoIII motifs.

Appellants submit that the amino acid sequences represented by SEQ ID NOs. 83-108 correspond to the wild type amino acid sequences of Archaeal DNA polymerases that were known in the art as of at least the filing date of the present application. Appellants submit that in the elected invention, the mutant Archaeal DNA polymerase comprises the recited mutations in the amino acid of SEQ ID NO. 89, which corresponds to the known, wild type amino acid sequence of *Pyrococcus furiosus* ("Pfu") DNA polymerase. Appellants submission is acknowledged and is in agreement with the above office's interpretation of the claimed breadth, in which the only structural limitations of the claimed DNA polymerase is with respect to the actual mutations themselves and not the remainder of the DNA polymerase structure.

Appellants submission that the exo I, II and III motifs are represented by the consensus amino acid sequences DXE, NX₂₋₃(F/Y)D and YX₃D, respectively, and that it

was also known in the art that DNA polymerases with 3' to 5' exonuclease activity, like Archaeal DNA polymerases, could be mutated in these conserved exo I, exo II, or exo III motifs to generate mutant DNA polymerases having reduced or abolished 3' to 5' exonuclease activity is acknowledged.

With respect to the elected invention (SEQ ID NO:89), appellants submit that the specification discloses several examples of mutant Pfu DNA polymerases comprising a mutation at V93, as well as other Archaeal DNA polymerases with deficient 3' to 5' exonuclease activity, including a Thermococcus sp. (JDF-3) DNA polymerase with a mutation at the position corresponding to D141 and/or E143 in the conserved exo I motif.

With respect to the non-elected invention (SEQ ID NOs. 83-88 and 90-108), appellants submit that, the specification discloses numerous examples of Archaeal DNA polymerases comprising a mutation at V93, including Pyrococcus sp. (Deep Vent), Therrnococcus gorgonarius (Tgo)6, Pyrococcus sp.(KOD)7, Therrnococcus litoralis (Vent), and Therrnococcus sp. (JDF-3). Appellants thus submit that given this guidance, one of skill in the art would be able to generate other mutant Archaeal DNA polymerases, such as mutant versions of SEQ ID NOs. 84-87, 91, and 94-108, having a mutation at V93.

It is noted that Appellants submitted examples of the elected mutant Pfu DNA polymerases each comprise the amino acid sequence of SEQ IDNO:89 with specific substitution mutations at position V93 of SEQ ID NO:89. It is further noted that as pointed out above Appellants claimed genus has no structural limitations outside of the

required mutation positions with respect to the actual type of mutation that is encompassed at the referred to structural positions. Further, as pointed out above at least one third of the known Archaeal DNA polymerase amino acid sequences that Appellants refer to relative to amino acid mutation V93, **do not** have a V93. While Appellants may submit that given an alignment of the elected SEQ ID NO:89 with these other non-elected non-V93 containing amino acid sequences, one of skill in the art could determine an amino acid position corresponding to V93 of the amino acid sequence, Appellants are reminded that appellants claims do not refer to the amino acid mutation of the claimed polymerase as that which “corresponds to V93”, but rather Appellants claims refer to “an amino acid mutation at V93” of an amino acid sequence selected from one of SEQ ID NO. 83-108. Of which SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:107 and SEQ ID NO:108 have no “V93”. Thus Appellants have certainly not described an amino acid mutation at V93 of SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:107 and SEQ ID NO:108. Further still Appellants have not described the significance of Appellants discovered mutation as being associated with amino acid position 93, a valine residue in this amino acid position or some other structural requirement. Thus Appellants have not adequately described the significance of V93 outside of the context of the amino acid sequence of SEQ ID NO:89.

The lack of an amino acid position V93 in greater than one third of the referred to amino acid sequences of SEQ ID NO:83-108 is evidence and provides reasoning that

the representative species that have a V93 are not sufficient in describing the breadth of the claimed genus.

Appellants submission that for the elected and non-elected inventions, one of skill in the art would recognize the common features as a mutation at V93 and at least one mutation in one or more of the conserved exo I, exo II, or exo III motifs in the amino acid sequences (SEQ ID NOs. 83-108) and a deficiency in 3' to 5' exonuclease activity is not persuasive on the basis that as discussed above, one of skill in the art would not recognize a mutation at V93 as a common feature as such a position does not exist in over one third of appellants cited sequences.

Appellants submission that the evidence shows that Appellants were in possession of the common features of not only the elected invention, but also of the full scope of the claimed genus, specifically the discovery of the mutation at V93 is not persuasive on the basis that as pointed out above at least one third of the known Archaeal DNA polymerase amino acid sequences that Appellants refer to relative to amino acid mutation V93, do not have a V93 to mutate.

Appellants submission that in addition to describing a sufficient number of representative species, the written description requirement for a claimed genus may be satisfied through disclosure of relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or some combination of characteristics. See MPEP §2163 is acknowledged.

With respect to function, as acknowledged above, the claimed mutant Archaeal DNA polymerase is deficient in 3' to 5' exonuclease activity, and as submitted by appellants, methods for assaying for such were known in the art and disclosed in the specification.

With respect to structure, as acknowledged above, the claims are drawn to a mutant Archaeal DNA polymerase comprising at least one mutation in one or more of the conserved exo I, exo II, or exo III motifs and a mutation at V93 in one of the wild type Archaeal DNA polymerases of SEQ ID NOs. 83-108, or in the case of the elected invention, SEQ ID NO. 89. Thus appellants claim 1 is drawn to a mutant DNA polymerase in which the only specified structural limitations are in regard to mutation positions (i.e. at least one amino acid mutation in the exoI motif and an amino acid mutation at V93). Outside of the structural limitations associated with each of the required two "at least one amino acid mutation" 's, the claimed DNA polymerase has no structural limitations.

Appellants submission that the claimed mutant polymerases are clearly defined by characteristics "other than the activities recited in the claims.", for example, in addition to reciting that the mutant Archaeal DNA polymerases are deficient in 3' to 5' exonuclease activity, claims 1-7 also recite that the mutant Archaeal DNA polymerase comprises an amino acid mutation at V93 and at least one amino acid mutation in the recited 3' to 5' exonuclease motifs in an amino acid sequence selected from one of SEQ ID NOs. 83-108, or in the case of the elected invention, SEQ ID NO. 89 is acknowledged, however, as pointed out above appellants claims merely limit structurally

the required mutation position and not even the type or extent of mutation of the claimed mutant DNA polymerase, if a "V93" existed. Further as over a third of the referred to Archaeal DNA polymerases do not have a V93, these amino acid sequences clearly support the unpredictability in the art.

Appellants submission that contrary to the Examiner' s unsupported assertions, there is a predictable structure for the recited function is not found persuasive on the basis that as discussed above with respect to V93, one third of the referenced amino acid sequences do not have a V93 and thus this is not by definition a predictable structure. Appellants submission that there was a known correlation in the art between the conserved exo I, exo II, and exo III motifs and 3' to 5' exonuclease activity is acknowledged, however, such does not remedy the lack of a predictable V93 structure.

Appellants question the previously made assertion that "at least one amino acid mutation..." effectively eliminates Appellants previously argued characteristics, such as the claims being directed to an Archaeal DNA polymerase comprising certain mutations. The examiner apologizes for any confusion in previously made statements. Those previously referred to statements were to intended to communicate the examiner's interpretation that the language which recites" An Archaeal DNA polymerase comprising at least one amino acid mutation..." effectively removes any limitation associated with a DNA polymerase being an Archaeal DNA polymerase on the basis that once an artisan mutates a protein, it is no longer that protein as it previously existed. It is now a mutant or variant of the protein that previously existed and as such the mutant or variant may have a structural relationship to that protein from which it originated, although it is not

required to have any structural relationship to the protein that previously existed. As discussed above Appellants claimed variant or mutant is required to have no structural limitations associated with its origin that is an Archaeal DNA polymerase.

Thus as stated above, claim 1 is interpreted as being drawn to a mutant Archaeal DNA polymerase which is deficient in 3'-5' exonuclease activity and comprises at least one amino acid mutation in the exo I motif, and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108. Thus for those reasons stated previously and above, Appellants claim 1 is drawn to a mutant Archaeal DNA polymerase which is deficient in 3'-5' exonuclease activity and comprising at least one mutation in the exol motif and an amino acid mutation at V93. Thus appellants claim 1 is drawn to a mutant DNA polymerase in which the only specified structural limitations are in regard to mutation positions (i.e. at least one amino acid mutation in the exol motif and an amino acid mutation at V93). Outside of the structural limitations associated with each of the required two “at least one amino acid mutation” ‘s, the claimed DNA polymerase has no structural limitations.

Appellants reference to comments made by the examiner for the first time in the Advisory action, related to “at least one amino acid mutation...” are acknowledged above, however, it is pointed out to Appellants that this language which the examiner was supposedly commenting on for the first time, is following Appellants after-final amendment of the claims in which, Appellants amended the claims from “An Archaeal DNA polymerase comprising an amino acid sequence selected from SEQ ID NOs. 83-108 and further comprising at least one amino acid mutation in the exol motif and

another amino acid mutation at V93..." to "An Archaeal DNA polymerase comprising at least one amino acid mutation in the exoI motif and another amino acid mutation at V93..." in the after-final amendment submitted by Appellants on 4/28/2009. Thus the supposed new emphasis on this language is a result of Appellants amendment in which Appellants have moved the referred to phrase within the context of the claim, thus potentially altering its meaning. It is noted that interestingly Appellants amendment after-final submitted on 4/28/2009, which was entered, resulted in the amendment of the claims from "An Archaeal DNA polymerase **comprising an amino acid sequence selected** from SEQ ID NOs. 83-108..." to "An Archaeal DNA polymerase **comprising at least one amino acid mutation** in the exoI motif and another amino acid mutation at V93...". This amendment appears to change the reference to SEQ ID NOs. 83-108 from that which the Archaeal DNA polymerase comprises to that which is a reference for the amino acid mutation positions. Appellants have not commented as to this amendment regarding the breadth of the claim

Appellants' submission that the Examiner's claim construction is erroneous on the basis that the examiner's construing the "at least one mutation..." language in claims 1-7 as eliminating the other recited elements of the claims is neither reasonable nor consistent with the specification and improperly reads out of the claims other express recitations, is acknowledged, however not found persuasive on the basis that as discussed above and previously the examiner continues to interpret that claim 1 is interpreted as being drawn to a mutant Archaeal DNA polymerase which is deficient in 3'-5' exonuclease activity and comprises at least one amino acid mutation in the exo I

motif, and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108. By virtue of appellants claims requiring that the Archaeal DNA polymerase be deficient in 3'-5' exonuclease activity, the claimed polymerase is no longer an Archaeal DNA polymerase, on the basis that as submitted by appellants, Archaeal DNA polymerases have a 3'-5' exonuclease activity. Outside of the structural limitations associated with each of the required two "at least one amino acid mutation" 's, the claimed DNA polymerase has no structural limitations.

As discussed above the "at least one mutation" language does not alter the known and disclosed correlation between exol, exoII and exoIII motifs and the 3'-5' exonuclease activity, however this is not the issue at the heart of the lack of written description. It is the lack of sufficient complete or partial structure, physical and/or chemical properties, method of making the claimed invention, level of skill in the art and the predictability in the art in the description of an Archaeal DNA polymerase comprising an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs.83-108. How can one describe such a genus of mutant DNA polymerases that do not exist, as none of SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:107 and SEQ ID NO:108 have a V93 which can be mutated.

Finally with regard to Appellants submission that the rejection should be withdrawn given the known wild type Archaeal DNA polymerase sequences recited in the claims (*i.e.*, SEQ ID NOs. 83-108, or in the case of the elected invention, SEQ ID NO. 89), Appellants are reminded that greater than one third of the amino acid

sequences cited by Appellants as supporting Appellants description of the claimed subject matter do NOT have a V93 and thus cannot support a claim to an Archaeal DNA polymerase comprising an amino acid mutation at V93. Further Appellants claimed genus remains sufficiently broad with no structural limitations outside of the recited mutation positions themselves that Appellants description of those DNA polymerase comprising SEQ ID NO: 89 with a V93 substitution mutation is insufficient to describe the claimed genus of any mutation at V93 selected from one or more amino acid substitutions, one or more amino acid insertions, a truncation or an internal deletion.

For the above reasons, it is believed that the rejections should be sustained.

Enablement

Appellants argue the rejection based upon a lack of scope of enablement on the following basis by addressing the Wands factors as interpreted by Appellants.

With regard to the **Breadth of the Claims**, Appellants submit that claims 1-7 are directed to mutant Archaeal DNA polymerases comprising at least one amino acid mutation in one or more of the conserved exo I, exo II, or exo III motifs and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOS. 83-108, where the Archaeal DNA polymerase is deficient in 3' to 5' exonuclease activity. Appellants submit that the sequences represented by SEQ ID NOS. 83-108 correspond to the known amino acid sequences of wild type Archaeal DNA polymerases. Appellants submit that according to the Examiner, the claims cover an infinite number of mutant Archaeal DNA polymerases.

Appellants submit that they do not understand the Examiner's reference to the "infinite number of mutant archaeal polymerases," however it appears this statement may be tied to the Examiner's erroneous claim construction discussed above in the written description section, and in particular to the Examiner's position that the claims cover "all possible mutant archaeal DNA polymerases." Appellants comments regarding the examiners **erroneous** interpretation of the claims are acknowledged, as are Appellants comments that "During prosecution, the Office must give claims their broadest reasonable construction, consistent with the specification. See MPEP § 2111."

As above under the rejection based upon a lack of written description, Appellants reference to the claims is appreciated and for the purpose of proper analysis of the enablement of the claimed subject matter, the breadth of these claims is discussed herein. Claim 1, for this purpose is directed to a mutant Archaeal DNA polymerase comprising: at least one amino acid mutation in the exo I motif, and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108, where said mutant Archaeal DNA polymerase is deficient in 3' to 5' exonuclease activity. It is understood that the claimed "Archaeal DNA polymerase" is deficient in 3'-5' exonuclease activity. Thus as Appellants have submitted that the Archaeal DNA polymerases have a 3' to 5' exonuclease activity (See appellants specification at page 1, line 22) appellants claim 1 is clearly drawn to a "mutant Archaeal DNA polymerase", which thus is not subject to any of the structural limitations of an "Archaeal DNA polymerase", because it is mutated such that it is no longer an "Archaeal DNA

polymerase". Claim 1 further recites that the claimed "Archaeal DNA polymerase" "compris(ing)es at least one amino acid mutation in the exol motif and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108". Thus the "mutant Archaeal DNA polymerase" comprises at least one amino acid mutation in the exol motif and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108. Thus, clearly the claimed mutant Archaeal DNA polymerase comprises at least two mutations that are not normally found in an Archaeal DNA polymerase. Appellants reference to "an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108, is interpreted as the referred to amino acid mutation is at position V93 in which V93 is referenced to SEQ ID NOs. 83-108. The reference to SEQ ID NOs. 83-108 is not interpreted as relevant beyond providing a reference to "V93" (See also discussion regarding Appellants amendment after-final submitted on 4/28/2008). Thus appellants claim 1 is drawn to an Archaeal DNA polymerase" which is deficient in 3'-5' exonuclease activity and comprises at lease two mutations that do not normally occur in an Archaeal DNA polymerase. One of the "at least one mutation" 's must be in motif I of the 3'-5' exonuclease domain and the other mutation must be at V93 of the elected SEQ ID NO:89 or the non-elected SEQ ID NOs:83-88 and 90-108. It seems that it should further be noted here that while the elected SEQ ID NO: 89 has a Valine residue at position 93 and thus a V93 which may according to appellants be further mutated, of the additional 25 SEQ ID NOs. referred to (i.e. SEQ ID NO. 83-88 and 90-108) 9 of these SEQ ID NOs do not have a valine at position 93 (i.e. SEQ ID NO:95, SEQ ID NO:96,

SEQ ID NO:99, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:106, SEQ ID NO:107 and SEQ ID NO:108, See appendix alignment of Appellants SEQ ID NOs 83-108). Thus 9 of the 25 non-elected SEQ ID NOs, which is greater than a third of the referenced group, do not have a V93.

Appellants noting that all of the recited sequences (SEQ ID NOs 83-108) are Family B/pol I type DNA polymerases, even though greater than a third of them do not have a V93 to mutate, is acknowledged and would appear to support the unpredictability in the art.

Additionally it is noted that appellants claim 1 is drawn to an "Archaeal DNA polymerase" comprising at least one mutation in the exoI motif and an amino acid mutation at V93 in the referred to amino acid sequence. These referred to mutations include but are not limited to one or more amino acid substitutions, one or more amino acid insertions, a truncation or an internal deletion (see specification page 11, lines 2-4). Appellants further specify that, as used herein, "mutant" polymerase refers to an Archaeal DNA polymerase, as defined herein, comprising one or more mutations that alter one or more activities of the DNA polymerase, for example, DNA polymerization, 3'-5' exonuclease activity or base analog detection activities (specification page 10, lines 23-26).

Thus, claim 1 is interpreted as being drawn to a mutant Archaeal DNA polymerase which is deficient in 3'-5' exonuclease activity and comprises at least one amino acid mutation in the exo I motif, and an amino acid mutation at V93 in an amino acid sequence selected from one of SEQ ID NOs. 83-108. Thus for those reasons

stated previously and above, Appellants claim 1 is drawn to a mutant Archaeal DNA polymerase which is deficient in 3'-5' exonuclease activity and comprising at least one mutation in the exol motif and an amino acid mutation at V93. Thus appellants claim 1 is drawn to a mutant DNA polymerase in which the only specified structural limitations are in regard to the specified mutation positions (i.e. at least one amino acid mutation in the exol motif and an amino acid mutation at V93). Outside of the structural limitations associated with each of the required two "at least one amino acid mutation" 's, the claimed DNA polymerase has no structural limitations. It is based upon this lack of sufficient structural limitations of the claimed genus of polymerases that the earlier phrase "infinite number of polymerases" was used, although it is appreciated that while rather large, it is likely that this number is not infinite. It is further noted that claims 2-7 are interpreted analogously to claim 1, as discussed above, however, with respect to the exolI and exolII motifs and combinations of the exol, exolI and exolII motifs.

As above Appellants reference to comments made by the examiner for the first time in the Advisory action, related to "at least one amino acid mutation..." are acknowledged, however, it is pointed out to Appellants that this language which the examiner is supposedly commenting on for the first time, is following Appellants after-final amendment of the claims in which, Appellants amended the claims from "An Archaeal DNA polymerase comprising an amino acid sequence selected from SEQ ID NOs. 83-108 and further comprising at least one amino acid mutation in the exol motif and another amino acid mutation at V93..." to "An Archaeal DNA polymerase comprising at least one amino acid mutation in the exol motif and another amino acid

mutation at V93..." in the after-final amendment submitted by Appellants on 4/28/2009. Thus the supposed new emphasis in this language is a result of Appellants amendment in which Appellants have moved the referred to phrase within the context of the claim, thus altering its meaning. It is noted that interestingly Appellants amendment after-final submitted on 4/28/2009, which was entered, resulted in the amendment of the claims from "An Archaeal DNA polymerase **comprising an amino acid sequence selected** from SEQ ID NOs. 83-108..." to "An Archaeal DNA polymerase **comprising at least one amino acid mutation** in the exoI motif and another amino acid mutation at V93...".

This amendment appears to change the reference to SEQ ID NOs. 83-108 from that which the Archaeal DNA polymerase comprises to that which is a reference for the amino acid mutation positions. Appellants have not commented as to this amendment regarding the breadth of the claims.

With regard to the **Nature of the Invention**, Appellants submit that they have discovered that a mutation at V93 within Archaeal DNA polymerases alters certain characteristics of the polymerases, such as uracil detection and that the V93 mutation can be combined with other mutations, such as one or more mutations within one or more of the conserved exo I, exo II, or exo III motifs in the 3' to 5' exonuclease domain of DNA polymerases. Appellants description of the Nature of the invention is confusing on the basis that if 9 of 26 Archaeal DNA polymerases cited by Appellants do NOT have a V93 to mutate (See SEQ ID NOs. 83-108 of Appellants specification and also the alignment of SEQ ID NOs 83-108 attached as an appendix), how can such a mutation at a position that does not exist alter certain characteristics of the polymerase.

With regard to the **State of the Art** at the time of filing of this application, Appellants submit that the art was well developed, both from the standpoint of mutagenesis schemes and from the standpoint of knowledge of Archaeal DNA polymerase structure and function. Indeed, the application cites numerous Archaeal DNA polymerases that, at the time of filing, had been sequenced and their respective sequences published, including the sequences recited in claims 1-7 (i.e., SEQ ID NOs. 83-108). Likewise, those of skill in the art were, at the time of filing, well aware of numerous methods for making and screening mutants of many different proteins.

Appellants characterization of the State of the Art is accurate, although it is noted that even given the well developed state of the art, the act of creating an amino acid mutation at V93 in an amino acid sequence that does not have a V93 (9 out of the 26 amino acid sequences cited by Appellants) is beyond the skill of the artisan without guidance as to the significance of V93 . That is guidance as to the structure to function significance of V93 is necessary to enable the scope of Appellants claimed genus. Specifically, is it the position 93, the valine at position 93 of SEQ ID NO: 89, the context of the valine at V93 or a combination thereof that is the basis of Appellants invention?

With regard to the **Level of Skill of Those of Skill in the Art** as indicated repeatedly by the Federal Circuit, the level of skill in the art of biotechnology is exceptionally high. The Examiner does not dispute this finding.

With regard to the **Level of Predictability in the Art**, Appellants admit that the Federal Circuit has asserted that biotechnology, at least at the time of filing of the present application, was an unpredictable art requiring an elevated level of disclosure

for enablement. Appellants submit that the present application has satisfied that heightened level of disclosure by providing numerous examples of Archaeal DNA polymerase mutants having a mutation at V93, each of which can be used by those of skill in the art as guides for developing additional mutants according to the claims.

Appellants submit that thus, although the art in general may be defined by the Federal Circuit as being unpredictable, the specific mutations recited in the claims are fully described.

Appellants characterization of the Level of Predictability in the Art is not accurate on the basis that Appellants have cited 26 amino acid sequences of wild-type Archaeal DNA polymerases, of which 9, greater than one third do not have a V93 to which an amino acid mutation can be made resulting in the desired functional alteration. Given that 17 of the cited amino acid sequences have a V93 and 9 DO NOT have a V93, there is no predictability as to whether an Archaeal DNA polymerase will have a V93 and Appellants specification does not remedy such.

Appellants submit that the 3'-5' exonuclease activity associated with proofreading DNA polymerases can be reduced or abolished by mutagenesis and sequence comparisons have identified three conserved domains (exo I (DXE), II (NX2.3(F/Y)D), III (YX3D) in the 3'-5' exonuclease domain of DNA polymerases (reviewed V. Derbyshire, J.K. Pinsonneault, and C.M. Joyce, Methods Enzymol. 262, 363 (1995)).
is persuasive with respect to the exoI, exoII and exoIII motif mutations exclusively, but as Appellants claims are not directed to merely these exo motif mutations, such is

insufficient to remedying the predictability of the existence of a V93 in an Archaeal DNA polymerase amino acid sequence.

With regard to the **Amount of Direction Provided by Appellants and the Existence of Working Examples**, Appellants submit that the claimed invention is clearly and fully described in the application, including not only specific mutations literally covered by the claims, but methods for making such mutations and methods of screening such mutations for expected activity. Furthermore, Appellants submit the specification provides numerous examples of Archaeal DNA polymerases having a mutation at V93, including a mutant Pfu DNA polymerase and that given the guidance in the specification and the well known mutagenesis methods, one of skill in the art would be able to generate other mutant Archaeal DNA polymerases having a mutation at V93.

Appellants comments regarding the amount of direction provided and the existence of working examples relative to the exol, exoII and exoIII motifs are appreciated and somewhat helpful, however, such direction and existence of working examples does not exist for an amino acid mutation at V93 of an amino acid sequence selected from one of SEQ ID NOs. 83-108, because as discussed throughout this Examiners Answer, 9 of those amino acid sequences presented by Appellants do not have a V93 which can be mutated and Appellants do not give any direction or working example to remedy this.

With regard to the **Quantity of Experimentation Needed to Make or Use the Claimed Invention**, Appellants submit that the Federal Circuit has made clear that the quantity of experimentation needed to make or use an invention is not dispositive of

enablement. Moreover, the test for undue experimentation is not merely quantitative, because a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (CCPA 1982); see also, *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1360, 47 USPQ2d 1705, 1719 (Fed. Cir. 1989) ("test [for undue experimentation] is not merely quantitative.., if it is merely routine.").

Appellants submit in the present situation, the number of mutants literally encompassed by the present claims is finite and defined by structure and that although many possible mutants are covered by the claims, it would be a matter of mere routine experimentation, much of which could be performed. Appellants assessment of Quantity of Experimentation Needed to Make or use the claimed invention is not accurate as the number of mutants literally encompassed by the present claims may be finite, they are defined by minor to little structure. Further still it is not routine experimentation to make an amino acid mutation at V93 of an Archaeal DNA polymerase when a V93 does not exist and Appellants have supplied no guidance that would make the quantity of Experimentation routine.

Thus, Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any Archaeal DNA polymerase comprising at least one amino acid mutation in an exoI, exoII or exoIII motif and

Art Unit: 1652

another amino acid mutation at position V93 in an amino acid sequence selected from SEQ ID NO:89 or the amino acid sequences of non-elected SEQ ID NOs: 83-88 and 90-108, wherein said polymerase is deficient in 3'-5' exonuclease activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Richard G Hutson/
Primary Examiner, Art Unit 1652

Conferees:

/Andrew Wang/

Supervisory Patent Examiner, Art Unit 1656

/Cecilia Tsang/

Supervisory Patent Examiner, Art Unit 1654

Art Unit: 1652

(12) Appendix

Alignment of amino acids 81-96 of SEQ ID NO:83-108 (SEQ ID NOS: 99, 102, 103, 107 and 108 include additional amino acids beyond position 96). V93 is bolded where it exists as are those valine residues located near position 93.

83	Glu Val Trp Lys Leu Ile Phe Glu His Pro Gln Asp Val Pro Ala Met	T. litoralis
	85 90 95	
84	Glu Val Trp Lys Leu Ile Phe Glu His Pro Gln Asp Val Pro Ala Leu	T. sp
	85 90 95	
85	Glu Val Trp Lys Leu Tyr Leu Glu His Pro Gln Asp Val Pro Ala Ile	P. abyssi
	85 90 95	
86	Glu Val Trp Lys Leu Tyr Leu Glu His Pro Gln Asp Val Pro Ala Ile	P. horikoshii
	85 90 95	
87	Glu Val Trp Lys Leu Tyr Leu Glu His Pro Gln Asp Val Pro Ala Ile	Pyrococc. sp.
	85 90 95	
88	Glu Val Trp Arg Leu Tyr Phe Glu His Pro Gln Asp Val Pro Ala Ile	Pyrococc. sp.
	85 90 95	
89	Thr Val Trp Lys Leu Tyr Leu Glu His Pro Gln Asp Val Pro Thr Ile	Pfu
	85 90 95	
90	Glu Val Trp Val Leu Tyr Phe Thr His Pro Gln Asp Val Pro Ala Ile	JDF-3
	85 90 95	
91	Glu Val Trp Lys Leu Tyr Phe Asn His Pro Gln Asp Val Pro Ala Ile	T. sp.
	85 90 95	
92	Glu Val Trp Lys Leu Tyr Phe Thr His Pro Gln Asp Val Pro Ala Ile	Pyrococc. sp.
	85 90 95	
93	Glu Val Trp Lys Leu Tyr Phe Thr His Pro Gln Asp Val Pro Ala Ile	T. sp.
	85 90 95	
94	Glu Val Trp Lys Leu Tyr Phe Thr His Pro Gln Asp Val Pro Ala Ile	T. fumicolans
	85 90 95	
95	Thr Glu Val Ile Arg Ile Glu Phe Arg His Pro Gln Asp Val Pro Lys	M. thermo
	85 90 95	
96	Val Lys Lys Ile Ile Leu Arg Lys Glu Lys Glu Val Ile Lys Ile Ile	M. jannas
	85 90 95	
97	Leu Asp Lys Arg Tyr Phe Gly Arg Pro Arg Lys Ala Val Lys Ile Thr	P. occultum
	85 90 95	
98	Leu Val Pro Ala Ser Val Arg Glu Tyr Arg Glu Ala Val Arg Arg Leu	Aero. pernix
	85 90 95	
99	Arg Glu Val Glu Gly Tyr Ile Val Tyr Ala His His Pro Gln His Val Pro Lys Leu Arg	
	85 90 95 100	
100	Glu Val Trp Lys Leu Tyr Phe Thr His Pro Gln Asp Val Pro Ala Ile	
	85 90 95	
101	Glu Val Trp Lys Leu Tyr Phe Asn His Pro Gln Asp Val Pro Ala Ile	
	85 90 95	
102	Arg Glu Val Glu Gly Tyr Ile Val Tyr Ala His His Pro Gln His Val Pro Lys Leu Arg	
	85 90 95 100	
103	Thr Asn Ile Glu Ile Ile Glu Lys Ile Val Tyr Ser Asp Tyr Ile Leu Asn Gly Lys Asp	
	85 90 95 100	
104	Lys Lys Phe Leu Lys Val Ile Ala Lys Ile Pro Glu Asp Val Arg Lys	
	85 90 95	

Art Unit: 1652

105	Ile Ala Asp Lys Asp Val Pro	Val	Thr Lys Ile Thr	Val	Ala Asp Pro
	85		90		95
106	Asp Glu Ser Gly His Lys Pro Tyr	Phe	Leu Thr Asp Ile Asp	Pro Asp Lys	Val Asn Lys
	85		90		95 100
107	Tyr Asp Asn Thr Gly His Lys Pro	Tyr	Phe Leu Thr Asp Ile Asp	Pro Glu Lys	Val Asn
	85		90		95 100
108	Tyr Asp Asn Thr Gly His Lys Pro	Tyr	Phe Leu	Val Asp Leu Glu	Pro Asp Lys
	85		90		95 100